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TD MR 1362
Project 4-08-03-05

A MEMORANDUM REPORT

AGENTS OF THE G SERIES
STUDIES IN THE CHEMISTRY OF ORGANOPHOSPHORUS COMPOUNDS
SECOND REPORT

By

Walter H. C. Rueggeberg

Jacob Chernack

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6 AGENTS OF THE G SERIES
STUDIES IN THE CHEMISTRY OF ORGANOPHOSPHORUS COMPOUNDS
SECOND REPORT

Submitted by: *Regraded*
by *W. H. C. Rueggeberg*
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ABSTRACT

Object.

The object of project 4-08-03-05 is, in part, to investigate the synthesis and properties of compounds of the G series.

The object of this report is to present data obtained from a series of reactions investigated during the course of a laboratory study on organophosphorus compounds. Several reactions anticipated to lead to the direct methylation of phosphorus trichloride drew particular attention.

Results.

1. Theories pertaining to the reactivity of phosphorus, both trivalent and pentavalent, toward nucleophilic and electrophilic reagents are discussed.
2. The direct methylation of phosphorus trichloride using anhydrous aluminum chloride as catalyst was investigated. A stable, highly reactive complex, consisting of methyl chloride, phosphorus trichloride and aluminum chloride in a mole ratio of 1:1:1, was isolated. It has not been found possible, to date, to isolate methylated chlorophosphines or their oxides from this complex using sulfur dioxide as reagent.
3. Triethyl phosphate was subjected to alcoholysis with butanol using sodium butoxide as catalyst. The products of reaction were mixed butyl ethyl phosphates, butyl ethyl ether, and small amounts of diethyl ether. The nature of the reaction, based on the supposition of the formation of a ten-electron intermediate, consisting of triethyl phosphate and butoxy ion, is discussed. The alkylating characteristic of triethyl phosphate toward primary and secondary amines, yielding ethyl alkylamines, is also discussed along similar lines.
4. Nine new compounds of the type $R_2N-PO(OR)_2$, dialkoxydialkylaminophosphine oxides, were prepared from the corresponding dialkyl hydrogen phosphites, carbon tetrachloride, and the corresponding dialkylamines. These substances showed no reaction in the indole fluorescent test for the G-type compound and possessed no toxic properties comparable to G agents.

Five analogs of GA and GB were synthesized and submitted to Medical Division for testing. These compounds were 2-chloroethoxycyanodimethylaminophosphine oxide, cyanodiethylaminomethoxyphosphine oxide, 2-chloroethoxydimethylaminofluorophosphine oxide, chlorocyanomethylphosphine oxide, and cyanoethylmethoxyphosphine oxide(not submitted for toxicity tests).

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5. The nature of the rearrangement of dimethylhydrogen phosphite to the corresponding phosphonic acid anhydride (pyro compound) was given some consideration in the light of available analogous data.

Conclusions.

1. Trivalent phosphorous compounds containing at least one phosphorous-to-chlorine bond are incapable of reacting with electrophilic reagents, such as alkyl halides, due to the positive nature of the phosphorus atoms in such phosphorus-chlorine compounds. This phenomenon has made direct alkylation of phosphorus trichloride impossible to the present day.

2. The alcoholysis of triethyl phosphate with butyl alcohol using sodium butoxide as catalyst results in the formation of mixed butyl ethyl phosphates and butyl ethyl ether. This phenomenon can be explained by assuming a ten-electron intermediate between the nucleophilic reagent, butoxy ion, and triethyl phosphate with subsequent decomposition of the complex to the observed products. The concept is strengthened by the fact that diethyl ether is also formed in this reaction.

3. The alkylation of amines by alkyl phosphates can also be accounted for by the assumption of the existence of a complex between triethyl phosphate and a primary or secondary amine (nucleophilic reagents).

4. The results of the alkylation studies make it appear that the rearrangement of dimethyl hydrogen phosphite follows a similar course of self-alkylation as is exhibited by the alkylation of amines and alkoxides by triethyl phosphate. This theory requires that dimethyl hydrogen phosphite is an equilibrium mixture of the trivalent and pentavalent forms.

Recommendations.

None, since work is being continued.

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ACKNOWLEDGEMENT

The authors are indebted to Messrs. N. Beitsch, S. Sass, and E. Zeffert for having performed the necessary analytical and physical determinations.

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AGENTS OF THE G SERIES
STUDIES IN THE CHEMISTRY OF ORGANOPHOSPHORUS COMPOUNDS
SECOND REPORT

I. INTRODUCTION.

A. Object.

The object of project 4-08-03-05 is, in part, to investigate the synthesis and properties of compounds of the G series.

The object of this report is to present data obtained from a series of reactions investigated during the course of a laboratory study on organophosphorus compounds. Several reactions anticipated to lead to the direct methylation of phosphorus trichloride drew particular attention.

B. Authority.

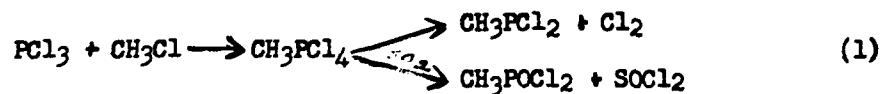
Authority for this work is contained in Project 4-08-03-05, Agents of the G Series, for fiscal year 1948.

II. HISTORICAL.

The historical aspects of this work have been described in previous reports and are summarized in their essential form in TDMR 1314, 30 April 1947.

III. THEORETICAL.

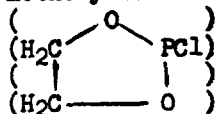
The theoretical aspects worthy of consideration are those connected with the direct alkylation of phosphorous trichloride by replacement of only one chlorine atom with the formation of either methyldichlorophosphine or its oxide. The following two hypothetical reactions serve to illustrate the desired reactions:



Numerous attempts, previously reported in TDMR 1314, have been made to realize both of these reactions without success. In essence, these reactions approximate the Arbusov type in nature; however, attempts to add

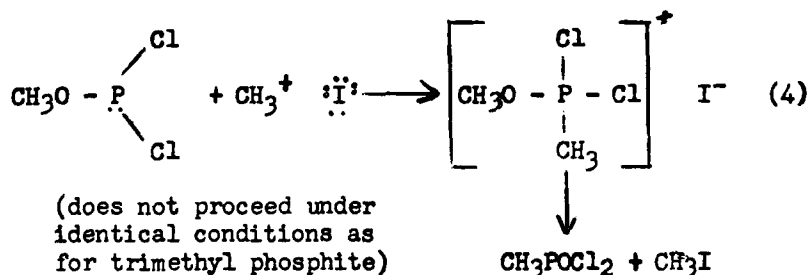
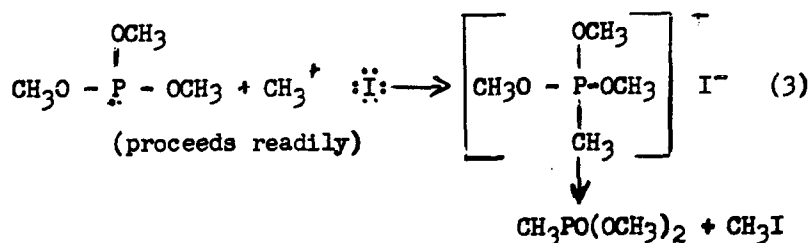
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alkyl halides to molecules such as methoxydichlorophosphine ($\text{CH}_3\text{O}(\text{PCl}_2)$) or 2-chloro-1,3,2-dioxaphospholane (



) gave only negative results with respect to alkylation by alkyl halides, the major products being those obtained from the decomposition of the reagents. These phenomena led the authors to the conclusion that trivalent phosphorus compounds bearing as small a number as one chlorine atom attached to phosphorus are incapable of direct alkylation of phosphorus.

Upon closer examination of the relation between structure and reactivity toward methyl iodide of trimethoxyphosphine and methoxydichlorophosphine, or even the phospholane stated above, it becomes apparent that the presence of one or more P-Cl linkage imparts a strong positive charge to the phosphorous atom in this type of molecule. The two contrasting reactions may be compared as follows:



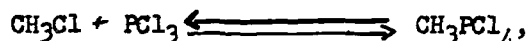
It appears that the positive charge on phosphorus, probably due to the strong dipolar effect of the P-Cl bond, is sufficiently strong to deny entry of a positive alkyl group, as the methyl group in methyl iodides, into the sphere of influence of the positive phosphorus atom.

On the other hand, those reagents in which the methyl group is negative, as is the case in metallic alkyls, alkylate phosphorus trichloride

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smoothly. Such reagents include the Grignard reagents, tetraalkyllead, dialkylmercury, etc. Although these substances form the desired products, not much emphasis has been placed on them, due to their relative inaccessibility and comparatively high cost.

Consideration was next given to the idea that in the reaction



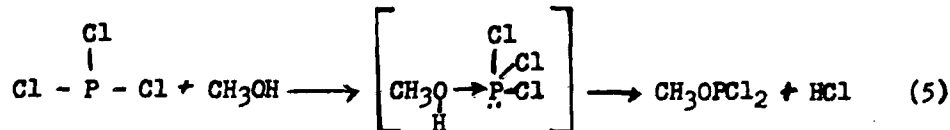
an equilibrium might exist favorable to the formation of tetrachloro compound. Subsequently, a number of catalysts was tried, which one might anticipate, would bind themselves with the product and so remove it from the equilibrium mixture. As shown in the body of this report, the use of anhydrous aluminum chloride produced some very interesting results, despite the fact that methylated phosphorus compounds, in particular methyldichlorophosphine oxide, could not be isolated.

The theory was then proposed that in compounds containing the P-Cl linkage, the phosphorus atom is highly electron deficient, in spite of the existence of a free electron pair, and that this electron pair is not available for reaction by electrophilic reagents. Furthermore, it appears that phosphorus in phosphorus trichloride is electrophilic, reacting smoothly with nucleophilic reagents. This is exemplified by the reactivities of metallic alkyls and alkyl iodides toward phosphorus trichloride, as stated above.

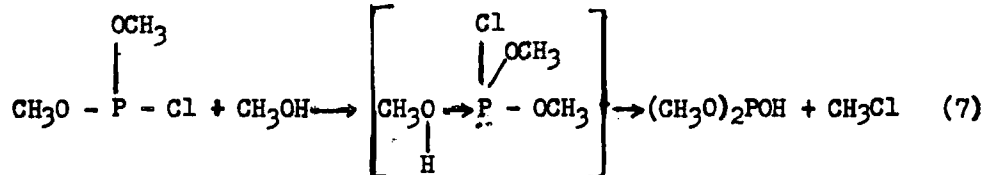
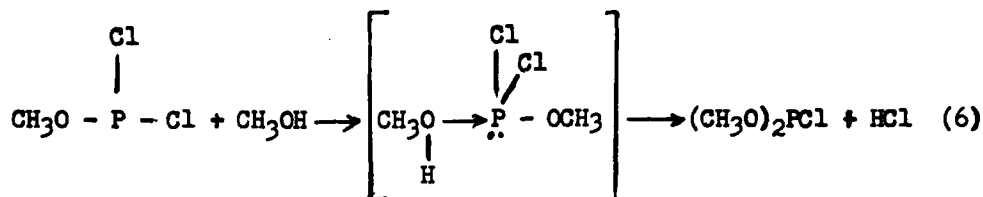
These facts allow then the separation of the reactivity of phosphorus trichloride or its immediate analogs into two classes:

- (1) Toward nucleophilic reagents
- (2) Toward electrophilic reagents

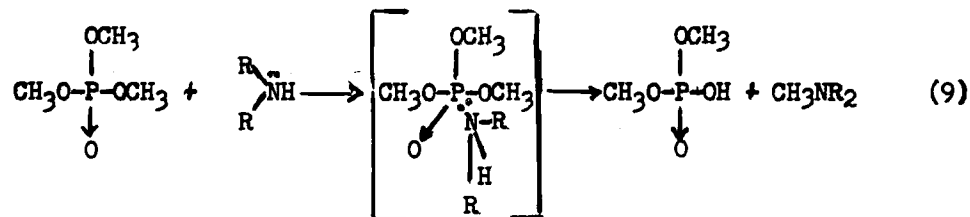
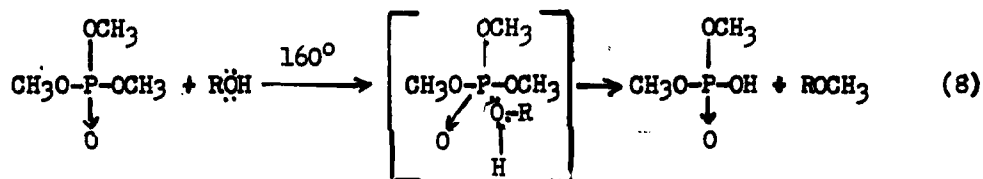
Although the reactions of phosphorus trichloride or its immediate derivatives toward electrophilic reagents are comparatively few, many of the known common reactions of phosphorus trichloride and, for that matter, of many trivalent and pentavalent organophosphorous compounds involving nucleophilic reagents can be explained by postulating a ten-electron intermediate. This intermediate, containing ten electrons around the phosphorus atom, will subsequently decompose or rearrange to produce the observed reaction products. The following known reactions can serve to illustrate this principle:



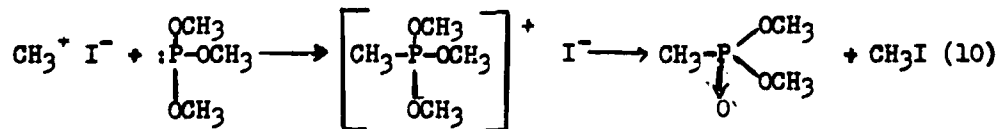
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Why dimethyl hydrogen phosphite is obtained as the final product in the absence of bases is not entirely clear; however, the energetics of the reaction are thought to be responsible for the formation of this compound. The trialkyl phosphite can be obtained from the ten-electron intermediate by the presence of an organic base which is capable of combining with HCl.



The additivity of alkyl halides to those organic molecules containing tri-valent phosphorus to which no halogen is bound, such as trialkylphosphines, trialkoxyphosphines, aminophosphines, etc., resembles the chemistry of analogous nitrogen compounds. The Arbuzov reaction is a typical example of this kind of reaction:



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IV. EXPERIMENTAL.

A. Materials.

All materials used in this work were purified before use to constant boiling point, composition, and physical constants.

B. Reaction of Methyl Chloride With Phosphorus Trichloride in the Presence of Anhydrous Aluminum Chloride.

To date, the direct combination of methyl chloride with phosphorus trichloride to form CH_3PCl_4 has not met with success. It was thought that perhaps the product was subject to an equilibrium unfavorable to the formation of the desired tetrachloride and being mainly on the side of the dissociated forms, methyl chloride and phosphorus trichloride. As a consequence, it was thought that a catalyst could conceivably direct the reaction toward the side of the undissociated tetrachloro form by combining with the latter in such a way that it would be removed from the equilibrium as a complex.

Anhydrous aluminum chloride was found to produce a complex of the composition $\text{CH}_3\text{Cl} \cdot \text{PCl}_3 \cdot \text{AlCl}_3$, from which no methylated phosphorus compound has as yet been isolated. The structure of the complex is not yet known, but, as indicated by the data in table 1, the composition clearly refers to a complex in which the $\text{CH}_3\text{Cl} \cdot \text{PCl}_3 \cdot \text{AlCl}_3$ ratio is 1:1:1.

The preparation of this complex can be achieved by sealing 0.05 mole of aluminum chloride, 0.05 mole of phosphorus trichloride, and 0.2 mole of methyl chloride (excess) in a suitable pyrex tube and allowing the reagents to come to room temperature. As the tube warms up, the solid aluminum chloride dissolves slowly in the liquid reagents with only a slight evolution of heat. The internal maximum temperature was estimated to be in the vicinity of 40°C . Shaking greatly accelerates the solution of aluminum chloride in the methyl chloride-phosphorus trichloride liquid mixture. After all the aluminum chloride has dissolved (and not before), a copious precipitation of well-defined crystals appears. Crystallization of the complex in the sealed tube was assumed to be complete after standing for about 30 hr. Each tube was subsequently chilled in a dry-ice-acetone mixture and opened. The effluent gases, consisting chiefly of excess methyl chloride, were condensed in a trap immersed in a dry-ice-acetone freezing mixture. The last traces of liquid were removed from the residue by applying a vacuum of approximately 20 mm. of Hg on the open end of the trap. The residue, consisting of the $\text{CH}_3\text{Cl} \cdot \text{PCl}_3 \cdot \text{AlCl}_3$ complex and the distillate, were analyzed as shown in table 1.

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Table 1

Preparation and Analyses of $\text{CH}_3\text{Cl} \cdot \text{PCl}_3 \cdot \text{AlCl}_3$ Complex

	Tube 1	Tube 2	Tube 3	Mean [†]	Theory
Amount of reagents used:					
Methyl chloride	0.2 mole or 10.1 g.				
Phosphorus trichloride	0.05 mole or 6.9 g.				
Aluminum chloride	0.05 mole or 6.7 g.				
Analysis of residue (complex):					
Weight of products, grams	16.3	15.0	15.6	15.60	16.1
Aluminum, %	8.95	8.44	8.67	8.69	8.39
Phosphorus, %	9.60	9.69	9.76	9.68	9.65
Chlorine, %	76.3	76.7	76.2	76.40	77.28
Carbon, %	3.5	3.4	3.5	3.47	3.74
Hydrogen, %	1.1	1.0	1.0	1.03	0.94
Total composition, %	99.5	99.2	99.1	99.27	100.00
Analysis of distillate:					
Weight of distillate, grams	5.9	5.5	5.4	5.6	7.6
P/total distillate	0.01	0.001	None	-	-
Cl/total distillate	0.1	0.27	0.06	-	-

Repeated attempts were made to isolate methyldichlorophosphine oxide from this complex by treatment with both gaseous and liquid sulfur dioxide. To date, this has not been achieved, one of the difficulties being the exclusion of aluminum chloride which is soluble to a considerable degree in SO_2 .*

*Since this report was written, a report (NRL P-3044) has been received which outlines a method for the separation of aluminum chloride using phosphoryl chloride as a complexing agent.

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C. Alcoholysis of Triethyl Phosphate Catalyzed by Sodium Butoxide and Alkylation of Amines (Morpholine) by Triethyl Phosphate.

Examples of the alcoholysis of esters derived from inorganic acids are not nearly so plentiful in the chemical literature as are those of the organic acid esters. Recently, the alcoholysis of alkyl silicates was studied by Peppard, Brown, and Johnson (¹). It was found that the alcoholysis of silicates proceeded in some cases without the addition of any catalyst to yield mixed silicic acid esters, but in those instances where no reaction was encountered in the absence of catalysts, the addition of silicon tetrachloride or hydrogen chloride was found to catalyze the reaction. A similar transalkylation reaction between butyl silicate and ethyl silicate under the catalytic influence of aluminum chloride or the alkoxides of aluminum, antimony, or magnesium was also found by these same authors (²) to produce mixed alkyl silicates.

Morel and Friedel (³) have shown that under the influence of sodium ethoxide, a mixture of ethanol and phenyl phosphate will yield mixed ethyl phenyl phosphates. These authors also discovered that phenetole is formed in the alcoholysis when three moles of sodium are used for every mole of phenyl phosphate. The latter property of alkylation is an interesting feature in this reaction and has been extended by Noller and Dutton (⁴). Toy (⁵) has found that methyl alkyl ethers can be prepared in 53-70% yield by boiling under reflux a mixture of trimethyl phosphate and alcohols. Some olefin formation is also encountered. The reaction is apparently limited to those alcohols which boil at 160°C. or higher at atmospheric pressure. The residue products in this reaction are described by Toy to be alkali-soluble mixtures of alkyl acid phosphates.

The reaction between 1-butanol and triethyl phosphate was studied in this laboratory with the view of obtaining butyl diethyl and dibutyl ethyl phosphates. It was observed that an equimolar mixture of triethyl phosphate and 1-butanol would not undergo appreciable reaction even at temperatures of about 160°C. In the presence of small amounts of sodium butoxide, however, alcoholysis proceeds rapidly at temperatures between 90° and 120°C. In table 2 it can be seen that the relative amounts of butyl diethyl phosphate and dibutyl ethyl phosphate depend upon the relative amounts of sodium butoxide present in the reaction mixture and also upon the mole ratio of ethyl phosphate to butanol-1. Some physical properties of the mixed esters are presented in table 3. The discrepancy between the parachors calculated from the values of Mumford and Phillips (⁶) and those found for both the butyl diethyl and dibutyl ethyl phosphates amounted to -4.4 and -7.3 units, respectively. At first it was thought that a rearrangement of the primary butyl group had occurred, yielding the secondary butyl phosphates; however, upon hydrolysis of the esters with hydrochloric acid only butyl chloride was found. The authors attribute these discrepancies to some factor in the values, not yet precisely determined, of the parachors of phosphorus groupings. A slight amount of

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impurity could have caused these deviations, but judging from the purity of the samples prepared, this cause was not apparent.

The entire operation was carried out in the kettle of a still having a plate equivalence of about fifteen. Upon heating the reaction mixture (see table 2), it was soon found that, in addition to the expected ethanol, other products were also formed. These substances proved to be ethers, of which butyl ethyl ether predominated. Splitting this ether with hydriodic acid yielded ethyl and butyl iodides. It is shown in table 2 that these ethers are formed not only when a large amount of sodium is present as was found by Morel and Friedel (3), but, in the particular case at hand, that these ethers are present to the extent of 21-24% of the ethanol-ether fraction removed, amounting to approximately one mole of ether for every mole of sodium.

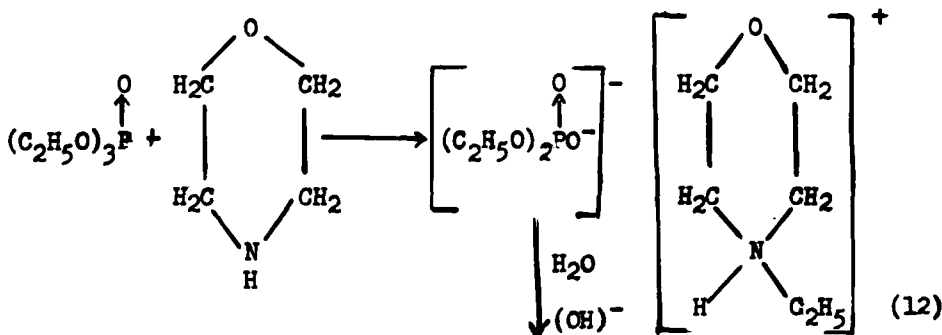
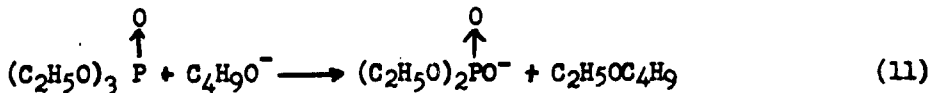
The presence of ethers suggests a dual character of triethyl phosphate, that of an ester and that of an alkylating agent. From the data in table 2, it will be seen that the mole ratio of ether to mixed butyl esters formed (calculated as difference between moles of butanol in the products and residue and moles of butanol originally used) is about 1 to 7. This means that sodium butoxide acts catalytically in the alcoholysis but is destroyed through ether formation. The destruction of the butoxy ion was also observed in separate experiments by noting the disappearance of phenolphthalein color in a small diluted sample of the reaction mixture. Ordinarily, this phenolphthalein test failed after the reaction mixture had been refluxed for 5 min. at 110°-120°C.

The still residue of the reaction is a white waxy solid contaminated with some of the mixed phosphate esters. An analysis of a reasonably dry, pure sample of the residue, after washing with ether, showed this to be a mixture of alkyl acid phosphates and their sodium salts as determined by the phosphorus, carbon, and hydrogen contents of this residue.

The alkylation of butoxy ion by ethyl phosphate is in many respects similar to the alkylation of aromatic amines studied by Billman, Radike, and Mundy (7). In order to establish the similarity between the alkylation of amines and of butoxy ion, the reaction of an equimolar mixture of morpholine and triethyl phosphate was investigated. It was found that upon heating, an oily nonvolatile substance, presumably an ammonium salt, was formed, which, upon hydrolysis with aqueous caustic, yielded pure 4-ethylmorpholine in 70% yield. Although amidation of the phosphoric acid ester, similar to alcoholysis, was not detected, this reaction may be of value in the de-alkylation of phosphoric acid esters (8).

These reactions may be summarized by the following equations:

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It is obvious from reaction (11) that small amounts of diethyl as well as dibutyl ether are to be expected through further reaction of the ethoxide and butoxide ions on the phosphates, and, indeed, traces of these are found.

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1. Alcoholysis of Triethyl Phosphate.

1-Butanol, clean metallic sodium, and triethyl phosphate were placed in the kettle of an all-glass, 15-plate column still in the order indicated. The amounts of reagents used in each particular run are given in table 2. Triethyl phosphate was not added to the other components until all the sodium had dissolved in the butanol. The complete reaction mixture was heated by means of a Glas-Col heating mantle. Boiling of the reagents occurred when the kettle temperature reached 115°C. The still head was set to constant reflux until boiling and the reflux rate became steady. Then, a low-boiling fraction (about 0.5 g., $n_D^{20} = 1.3655$, probably diethyl ether) was removed. The fraction boiling from 36° to 93°C. was collected and found to be a mixture of ethanol and chiefly butyl ethyl ether, containing from 75 to 80% ethanol as found by acetylation with acetic anhydride. The refractive index of these cuts varied between $n_D^{20} = 1.365$ to 1.368 and the densities, d_{20} , from 0.780 to 0.788 g./ml. During the removal of this fraction, the kettle temperature rose slowly to 140°C., and on occasions the temperature was allowed to climb to 160°C. in order to remove all this fraction at atmospheric pressure.

The pressure was subsequently reduced to 50 to 60 mm. of mercury, and 1-butanol ($n_D^{20} = 1.390$ to 1.398) was removed. After removing unreacted triethyl phosphate at pressures varying between 3 and 10 mm. of mercury (b.p. 66° to 69° at 3 to 4 mm. Hg; $n_D^{20} = 1.404$ to 1.4055), butyl diethyl phosphate (b.p. 82° to 87° at 3 to 4 mm. Hg) and dibutyl ethyl phosphate (b.p. 95° to 96° at 3 to 4 mm. Hg) were fractionated from the reaction mixture. Analysis: Calculated for $C_8H_{19}PO_4$: P, 14.7; M_{RP} , 51.5. Found: P, 14.9; M_{RP} , 51.1*. Calculated for $C_{10}H_{23}PO_4$: P, 13.2; M_{RP} , 60.5. Found: P, 13.2; M_{RP} , 59.8.*

The material balances in all runs including residues amounted to 97 to 99% of theory.

2. Isolation of Butyl Ethyl Ether.

Fifty grams of the ethanol-ether fraction (b.p. 36° to 93°C.) was added to 180 ml. of water. The upper layer, amounting to 8.9 g., was separated, dried over activated silica gel, and distilled. The main fraction boiled at 90° to 93°C. and was found to have the following constants: d_{20} , 0.752; n_D^{20} , 1.3818; M_{RP} , calcd., 31.6; M_{RP} found, 31.6. Analysis: calculated for $C_6H_{14}O$: C, 70.5; H, 13.8. Found: C, 70.6; H, 13.9. The ether so obtained was refluxed with 10% excess concentrated hydriodic

*The molecular refractivities were calculated from that of triethyl phosphate by adding the proper value for the required number of methylene groups to that molecule.

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acid. The reaction product was poured into water and decolorized with sodium bisulfite. The organic layer was separated and dried. Distillation yielded ethyl iodide (boiling range 75° to 87°C.), some unreacted ether (boiling range 87° to 97°C.), and butyl iodide (b.p. 125° to 129°C.), whose refractive index (n_D^{25}) was found to be 1.4950.

3. Butyl Chloride From Dibutyl Ethyl Phosphate.

One mole of dibutyl ethyl phosphate was refluxed with a 100% excess of concentrated hydrochloric acid for 8 hr. At the end of this time, the product was poured into water and extracted several times with diethyl ether. The ether extracts were dried over calcium chloride and distilled. After removing the ether, the residue distilled at 77° to 78°C. and had a refractive index, n_D^{25} , of 1.3991.

4. Alkylation of Morpholine.

An equimolar mixture of morpholine and triethyl phosphate was placed in a round-bottom flask equipped with a water-cooled reflux condenser. The mixture was heated by means of a Glas-Col mantle and brought to 150°C. in 15 to 20 min. At this temperature vigorous refluxing took place due to heat of reaction, and the mixture changed from a water-white to a reddish brown color. If too well insulated, the temperature of the reactants may rise to 190°C. It was found, however, that by maintaining the reaction temperature between 157° and 159° C., good results could be obtained. The product was poured into 500 ml. of water and heated with 10% excess (44 g.) of sodium hydroxide. The basic aqueous solution was placed in a still, and the amine distilled with water as an azeotrope over the range 95° to 99.8°C. The azeotropic distillate was saturated with potassium carbonate, whereupon the amine was salted out. After separation from the aqueous layer, the amine was dried over sodium sulfate, filtered, and distilled. Its physical constants were as follows: b.p., 137° to 138°C.; d_{20}^{20} , 0.919; n_D^{20} , 1.4418. Yield, 70%. Analysis: Calculated for $C_6H_{13}NO$: C, 62.2; H, 11.4; N, 12.2. Found: C, 62.3; H, 11.5; N, 11.9.

All physical constants given for known compounds agree satisfactorily with those previously published.

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Table 2

Alcoholysis and Ether Formation With Ethyl Phosphate

Reagents			Products						Residue
BuOH	Na	Et ₃ PO ₄	EtOH*	Et ₂ O*,**	BuOH	Et ₃ PO ₄	3uEt ₂ PO ₄	Bu ₂ EtPO ₄	
moles	moles	moles	moles	moles	moles	moles	moles	moles	g.
1.0	0.03	0.5	0.18	0.02	0.81	0.32	0.12	-	12.3
1.0	0.07	0.5	0.50	0.06	0.51	0.14	0.19	0.06	24.1
1.0	0.13	0.5	0.55	0.08	0.37	0.10	0.16	0.08	36.9
2.0	0.13	0.5	0.76	0.11	1.09	0.04	0.12	0.15	-
3.0	0.13	0.5	0.77	0.09	2.16	0.02	0.13	0.15	43.9
3.0	0.22	0.5	0.90	0.14	1.98	0.01	0.06	0.12	-

* The total ethanol-ether fraction from the distillation was subjected to a separate analysis for per cent alcohol, using acetic anhydride and pyridine, followed by titration for acid in the usual manner.

** This is chiefly butyl ethyl ether, containing less than 2% of a material boiling between 33° and 35°C., which possessess all characteristics of ethyl ether.

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Table 3

Some Physical Constants of Mixed Butyl Ethyl Phosphates

Temperature	Butyl Diethyl Phosphate*			Dibutyl Ethyl Phosphate**		
	d_T	n_D	Viscosity	d_T	n_D	Viscosity
°C.	g./ml.		centistokes	g./ml.		centistokes
9.8	-	-	2.73	-	-	3.76
10.0	1.0380	1.4170	-	1.0112	1.4215	-
20.0	-	1.4131	-	-	1.4182	-
24.7	-	-	1.97	-	-	-
25.0	1.0243	-	-	0.9984	-	2.54
30.0	-	1.4091	-	-	1.4148	-
35.0	1.0151	-	1.61	0.9897	-	2.05

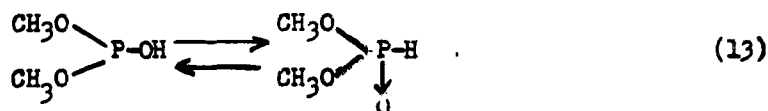
* Surface tension at 27.0° = 28.8 dynes/cm.; parachor, calculated 480.7, found, 476.3.

** Surface tension at 29.2° = 28.0 dynes/cm.; parachor, calculated 560.7, found, 553.4.

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D. Attempted Alkylation of Dimethyl Hydrogen Phosphite With Triethyl Phosphate.

In view of the alkylating property of triethyl phosphate toward alcohols, alkoxides, and amines, described in section IV, B, above, it appeared worthwhile to consider the reaction between triethyl phosphate and dimethyl hydrogen phosphite. For this purpose it must be assumed that dimethyl hydrogen phosphite is an equilibrium mixture consisting of the following two forms:



This assumption is justified, since reactions of dialkyl hydrogen phosphites can be cited in which one structure is to be preferred over the other, while in other reactions the alternate structure is the better. A longer discussion of this phase of the theory is given in section V of this report.

One-half mole of triethyl phosphate and 0.45 mole of dimethyl hydrogen phosphite were heated at reflux temperature for 3 da. (total heating time about 24 hr.). At the end of this period, a fairly viscous mass was obtained, and the temperature of the flask contents rose from 192° to 200°C. During the heating period small samples were taken at certain intervals and analyzed for their content of trivalent phosphorus by titration with 0.1 N iodine. The results are given in table 4.

Table 4

Trivalent Phosphorus Content of Dimethyl Hydrogen Phosphite-Triethyl Phosphate Mixture

<u>Time of heating</u> <u>hr.</u>	<u>Trivalent P in reaction mixture</u> <u>%</u>
0	28
15	14
24	4.5

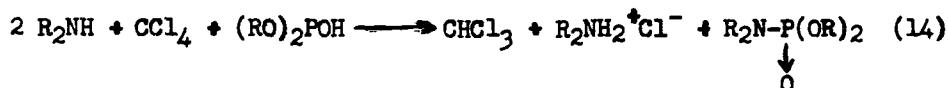
This type of work needs to be continued in order to establish the nature of the products formed. It is not as yet known, for example, whether the loss of trivalent phosphorus is due to the alkylation of dimethyl hydrogen phosphite by triethyl phosphate, or whether triethyl phosphate simply acts

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as an inert medium for the rearrangement of the phosphite as usually carried out in Nujol or other liquid media. The opinion of the writers is, however, that it is a reaction of the phosphite with the phosphate. Further work of this kind is recommended to aid in the elucidation of the mechanism of rearrangement dimethyl hydrogen phosphite to the pyro compound.

E. Preparation of Dialkoxydialkylaminophosphine Oxides.

In order to supply Medical Division with a variety of organophosphorus compounds differing in their structure, a series of dialkoxydialkylaminophosphine oxides* was prepared by the method of Atherton, Openshaw, and Todd (9).



The synthesis used for all of these compounds is exemplified by the following typical run:

One-half mole of dibutyl hydrogen phosphite, 1.1 mole of dimethylamine, and 200 ml. of benzene were placed in a 3-neck 500-ml. round-bottom flask, equipped with stirrer, thermometer, and dropping funnel. The flask contents were cooled to 10° to 20°C. by means of an ice-water bath. Then 0.55 mole (10% excess) of carbon tetrachloride was added from the dropping funnel to the stirred reaction mixture at such a rate that the temperature was maintained at 25°C. The reaction mixture was allowed to cool to room temperature, and the amine hydrochloride was filtered off with suction. The filtrate was treated with 10 ml. of carbon tetrachloride, followed by 10 g. of dimethylamine. A negative test (no appearance of crystals) indicated the completeness of the reaction. The volatile material was then stripped from the liquid residue by distillation at temperatures up to about 90°C. under a vacuum from a water aspirator. The residue was filtered again to remove a small amount of amine hydrochloride which crystallized in the concentration step. The crude dibutoxydimethylaminophosphine oxide is distilled under a vacuum of 2 mm. or less.

Table 5 is a summary of the data obtained in a similar fashion for analogous compounds using the same method of preparation.

It should be noted that the indole-fluorescence test (10) was performed on each of these compounds and was found to be negative or virtually so. This is in agreement with the low toxicity exhibited by

*Due to the lack of a method of nomenclature universally acceptable, it has been found desirable to use the nomenclature cited for its simplicity.

Table 5

Physical Properties and Analyses on Dialkoxodialkylaminophosphine Oxides *

Formula	Fluorescence test (a)	Molecular weight	Boiling point °C./mm. Hg	Nitrogen		Phosphorus		Mol. refractivity Calcd.	Refractive index, _D ²⁰	Density d ₂₀	Solution in water
				Theory	Found	Theory	Found				
	N	195.16	117.0-117.5/7	7.18	6.97	15.87	15.96	43.59	1.4522	1.222	g./ml.
	N	251.26	114-115/4.5	5.58	5.61	12.33	12.45	62.07	1.4418	1.069	%
	N	265.33	121-122/5.5	5.28	5.29	11.68	11.87	71.93	1.4315	0.966	0.5
	N	237.28	87.5-93/4.6	5.90	5.86	13.06	13.54	62.69	1.4201	0.961	5+
	N	181.13	75-76/5.5	7.73	7.58	17.10	17.43	44.21	1.4253	1.065	
	V.v.s.	153.12	89-94/24-32	9.15	9.06	20.23	20.48	34.97	1.4182	1.125	
	N	209.22	49-58/2.4	6.70	6.68	14.81	15.01	53.45	1.4150	0.989	
	N	237.27	81-85/0.5-2.0	5.90	5.88	13.06	13.18	62.69	1.4284	0.989	about 1-2
	V.v.s.	110.06	50-54/9-10	-	-	28.15	28.18	22.17	1.4021	1.202	

(a) The indole fluorescence test for G agents was tried on these compounds.

N = Negative test results.

V.v.s. = Very, very slightly positive test.

*These preparations were made by Mr. I. Rose, formerly of this lab.

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these compounds as determined by Medical Division (11).

In one run, chloroform was isolated from the reaction mixture. It was found to possess the following characteristics in agreement with accepted values in the chemical literature:

Boiling point = 61.3° to 61.8°C.
Refractive index, n_D^{20} = 1.4460
Density, d_{23}^{20} = 1.491 g./ml.

F. Preparation of Some G Analogues and Their Intermediates.

$$\begin{array}{c} \text{O} \\ \uparrow \\ \text{CN} \end{array}$$
 1. Synthesis of $(\text{CH}_3)_2\text{N}-\text{P}-\text{OCH}_2\text{CH}_2\text{Cl}$.

This compound was prepared by the dropwise addition of dichlorodimethylaminophosphine oxide (0.75 mole) to a well-stirred slurry containing sodium cyanide (2.13 mole), 2-chloroethanol (0.81 mole), and dry benzene (180 ml.). The reaction temperature was maintained at 40°C. After the addition was complete, the reaction mass was heated at 40°C. for 1 hr., cooled to room temperature, and the salts were filtered off using suction. The solid was washed with two 75-ml. portions of dry benzene. The filtrate and washings were combined, and the solvent was removed under reduced pressure (80 to 100 mm. of Hg). Distillation of the residue gave a product boiling at 116° to 117°C. at 1 to 2 mm. Analysis: Calculated for $\text{C}_5\text{H}_{10}\text{ClNO}_2\text{P}$: C, 30.54; H, 5.1; CN, 13.23; N, 14.25. Found: C, 30.56; H, 5.2; CN, 12.84; N, 14.62.

$$\begin{array}{c} \text{O} \\ \uparrow \\ \text{CN} \end{array}$$
 2. Synthesis of $(\text{CH}_3)_2\text{N}-\text{P}-\text{OCH}_3$.

This compound was prepared using procedure similar to that outlined above. The starting material for this reaction was chlorodiethylaminophosphine oxide, sodium cyanide, and methanol. The product boiling at 95° to 96°C. at 3 mm. was analyzed. Analysis: Calculated for $\text{C}_4\text{H}_9\text{N}_2\text{O}_2\text{P}$ = CN, 14.78; N, 15.91. Found: CN, 14.60; N, 15.64.

$$\begin{array}{c} \text{O} \\ \uparrow \\ \text{F} \end{array}$$
 3. Synthesis of $(\text{CH}_3)_2\text{N}-\text{P}-\text{OCH}_2\text{CH}_2\text{Cl}$.

To a well-stirred slurry of 120 g. of potassium acid fluoride in 400 ml. of dry benzene was added 95 g. of 2-chloroethoxycyanodimethylamino-

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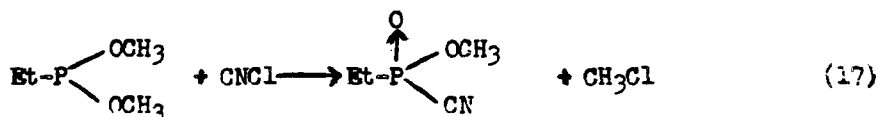
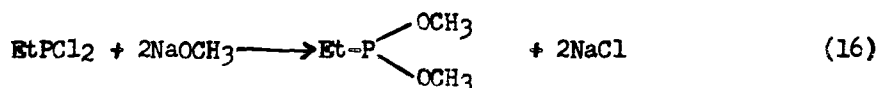
phosphine oxide in 100 ml. of benzene. The temperature was maintained at 70 to 75 °C. for 12 hr. The salts were filtered off under suction and washed with two 50-ml. portions of benzene. After removal of the solvent, the material was distilled at 71° to 73°C. at 1 to 2 mm. Analysis: Calculated for C_2H_3ClNOP : N, 7.39; Cl, 18.70. Found: N, 7.39; Cl, 18.58.

$\begin{array}{c} O \\ \uparrow \\ CN \end{array}$
 4. Synthesis of CH_3P-Cl .

Equal quantities of silver cyanide and methyldichlorophosphine oxide in 500 ml. of dioxane were heated to reflux temperature with vigorous stirring for 25 hr. The solid material was filtered off and washed with two 100-ml. portions of dioxane. After combining the washings and the filtrate, the solvent was removed under reduced pressure. The residue was fractionated and yielded approximately 10 to 25% of a product boiling at 87 to 89°C. at 21 mm. Analysis: Calculated for C_2H_3ClNOP : N, 7.39; Cl, 18.70. Found: N, 7.39; Cl, 18.58.

$\begin{array}{c} O \\ \uparrow \\ CN \end{array}$
 5. Synthesis of CH_3P-OCH_3 .

This compound was prepared through the following series of reactions:



The procedure for reaction (15) is described in OSRD 5483. Reaction (16) was performed in the following manner:

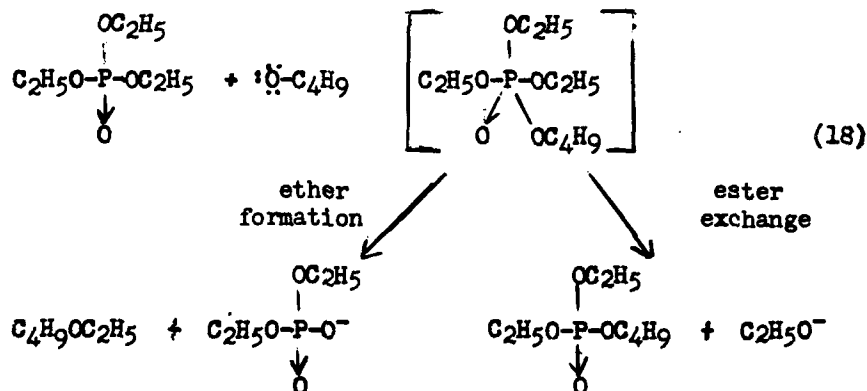
Ethyldichlorophosphine (0.46 mole) was added dropwise to a stirred mixture of sodium methoxide (0.96 mole) in 500 ml. of absolute ether in an inert atmosphere. The addition rate was adjusted so that the ether refluxed gently. After 4 hr. the reaction mass was cooled to room temperature and filtered. The solid was washed with two 50-ml. portions of ether. The

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combined washings and filtrate were stripped and the residue was distilled in a nitrogen atmosphere. Its boiling point was 71° to 72°C. at 210 mm. Analysis: Calculated for $C_4H_{11}O_2P:OCH_3$, 50.8. Found: OCH_3 , 50.7. In the final step of this synthesis, 20 g. of cyanogen chloride in 50 ml. of benzene was added dropwise to 26.5 g. of dimethoxyethylphosphine in 150 ml. of benzene. A temperature of 40° to 45°C. was maintained by cooling the reaction flask. After 1½ hr. the solvent was stripped and the residue was fractionated. Its boiling point was 83° to 85°C. at 9 mm. and 76° to 78°C. at 7 mm. Analysis: Calculated for $C_4H_8NO_2P:CN$, 19.56; N, 10.52. Found: CN, 18.49; N, 9.71.

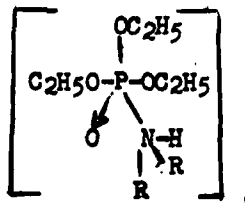
V. DISCUSSION.

The products of alcoholysis of triethyl phosphate using sodium butoxide can be accounted for by postulating the formation of a ten-electron intermediate as given for several other reactions in the theoretical section of this report.



As pointed out in the experimental section of this report, the formation of ethyl ether can be accounted for by repetition of the same mechanism, using, however, the ethoxy ion as the nucleophilic reagent.

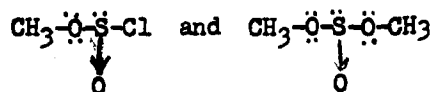
Similarly, the alkylation of a primary or secondary amine can be postulated to proceed through a ten-electron intermediate of the following structure,



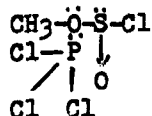
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which decomposes subsequently to the ethylated amine. Trialkylamines have not yet been tried, but it is supposed that by a similar de-alkylation procedure of the phosphate, a tertiary amine could be converted to a quaternary ammonium salt.

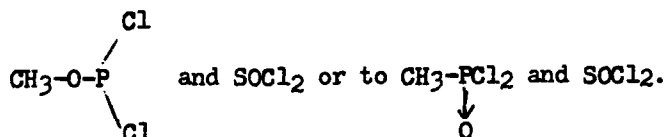
Some thought has been given to the reaction of phosphorus trichloride with certain nucleophilic reagents, which could conceivably alter the positive charge on the phosphorus atom, so that the phosphorus would become sufficiently negative to become capable of reacting with electrophilic reagents, especially methyl groups. One such system devised was the esters of sulfurous acid:



A ten-electron complex was predicted of the following electronic configuration:



which was suspected to be capable of decomposing to either



To date, laboratory investigations* have shown that $\text{CH}_3-\text{O}-\text{S}-\text{Cl}$

will not react appreciably with phosphorus trichloride but that $\text{CH}_3\text{O}-\text{S}-\text{O}-\text{CH}_3$

will react and produce CH_3OPCl_2 , sulfur dioxide, and methyl chloride. This reaction is being studied further.

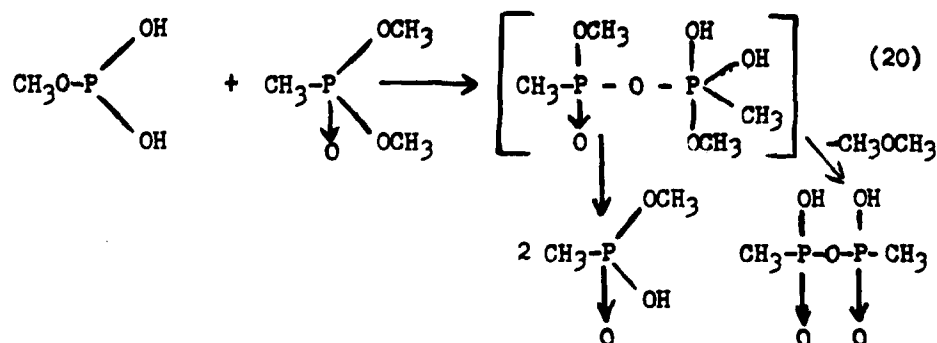
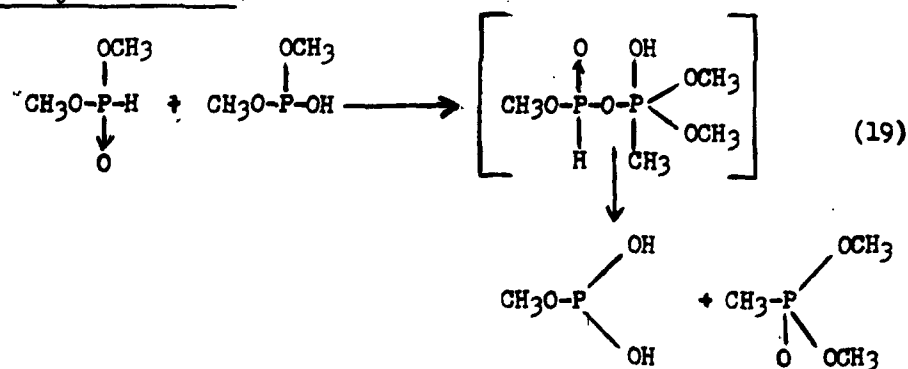
*These experiments were performed by Mr. T.P. Dawson of this Command.

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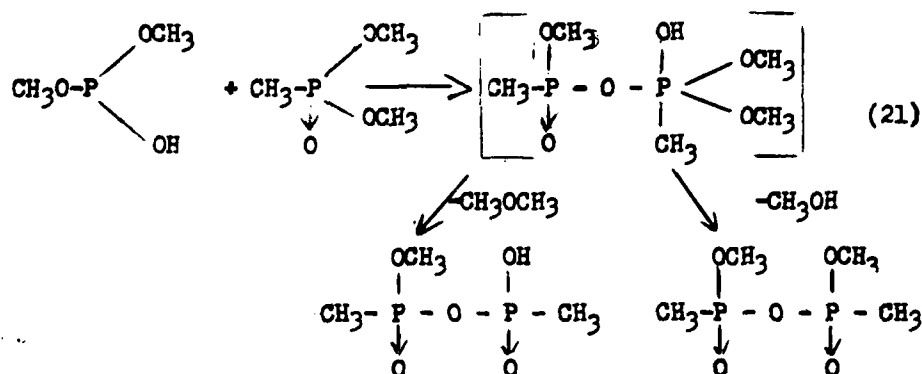
The alkylating properties of alkyl phosphates, as, for example, triethyl phosphate, is believed to be of considerable significance in the rearrangement of dimethyl hydrogen phosphite. Attention is called to the reaction between dimethyl hydrogen phosphite and triethyl phosphate described in the body of this report, in which a constant decrease of trivalent phosphorus is encountered as a function of time. It is realized, of course, that the exact nature of the disappearance of trivalent phosphorus in this reaction is not fully understood, that is, whether this decrease of trivalent phosphorus is due to alkylation of the phosphite by phosphate or whether it is due to the spontaneous rearrangement of dimethyl hydrogen phosphite in the medium, triethyl phosphate.

In either case, the alkylating properties of phosphates on nitrogen and oxygen allow the supposition that one conceivable series of mechanisms of rearrangement of dimethyl hydrogen phosphite is the following, assuming, as before, the equilibrium between a trivalent and pentavalent form of dimethyl hydrogen phosphite:

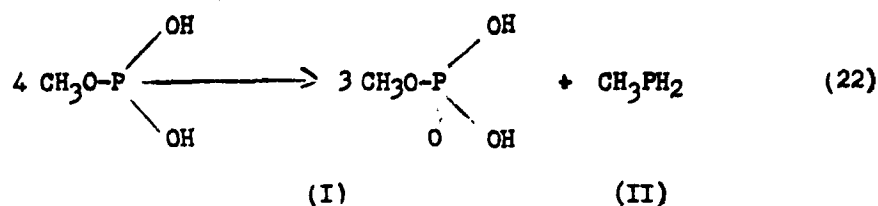
Probable Major Reactions:



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Probable Minor Reaction:

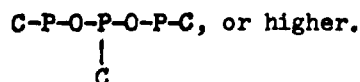


Note:

Product I would appear as POCl_3 on chlorination.
 Product II has never been reported to be present to the best of the authors' knowledge.

Whether this mechanism is correct cannot be stated at this time; however, the alkylated products, as well as the formation of methyl alcohol, dimethyl ether, and some unalkylated pentavalent phosphate, all of which have been encountered in practice, are accounted for. Other similarly valid reactions could no doubt be written to represent the scheme of things in this rather complicated arrangement.

It is also conceivable that anhydrides of higher molecular weight might be present, i.e., those polymers which contain linkages of the type:



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This type of anhydride would probably give the same end-product, CH_3POCl_2 , on chlorination.

VI. CONCLUSIONS.

1. Trivalent phosphorus compounds containing at least one phosphorus-to-chlorine bond are incapable of reacting with electrophilic reagents, such as alkyl halides, due to the positive nature of the phosphorus atoms in such phosphorus-chlorine compounds. This phenomenon has made direct alkylation of phosphorus trichloride impossible to the present day.

2. The alcoholysis of triethyl phosphate with butyl alcohol using sodium butoxide as catalyst results in the formation of mixed butyl ethyl phosphates and butyl ethyl ether. This phenomenon can be explained by assuming a ten-electron intermediate between the nucleophilic reagent, butoxy ion, and triethyl phosphate with subsequent decomposition of the complex to the observed products. The concept is strengthened by the fact that diethyl ether is also formed in this reaction.

3. The alkylation of amines by alkyl phosphates can also be accounted for by the assumption of the existence of a complex between triethyl phosphate and a primary or secondary amine (nucleophilic reagents).

4. The results of the alkylation studies make it appear that the rearrangement of dimethyl hydrogen phosphite follows a similar course of self-alkylation as is exhibited by the alkylation of amines and alcohols by triethyl phosphate. This theory requires that dimethyl hydrogen phosphite is an equilibrium mixture of the trivalent and pentavalent forms.

VII. RECOMMENDATIONS.

None, since work is being continued.

VIII. BIBLIOGRAPHY.

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10. B. Gehauf and J. Goldenson, TMR 1317, Analysis and Detection of G Compounds by Fluorometric Methods. Indole-Peroxide Method.
11. Personal communication from Dr. Leonard Karel of Medical Division.

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